I. SYNTHETIC ANTIMALARIALS
II. STEREOCHEMISTRY OF 2-SUBSTITUTED BIPHENYLS

BY

ROBERT OLVIN SAUER

B. A., Coe College, 1936

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
UNIVERSITY OF ILLINOIS, 1940

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I. SYNTHETIC ANTIMALARIALS
II. STEREOCHEMISTRY OF 2-SUBSTITUTED BIPHENYLS

I. *Synthetic Antimalarials of the 9-Dialkylaminoalkylamina-4-phenylacridine Type.*

The synthesis of atebrin,[1] 2-methoxy-6-chloro-9-(δ-diethylamino-α-methylbutylamino) acridine dihydrochloride, and its discovery[2] as a much more effective schizonticidal drug than quinine in the treatment of malaria has caused increased interest in the effectiveness of other drugs of similar structure. This research reports the synthesis of two 9-dialkylaminoalkylamino-3-chloro-5-phenylacridines and experiments on the preparation of 2-chloro- and 2-methoxy-4-phenyl-6-chloro-9-(δ-diethylamino-α-methylbutylamino) acridines.

Experimental

γ-(N-Morpholino) propylamine was prepared from 1,3-dibromopropane by condensation first[3] with one mole of potassium pthalimide and then with morpholine, followed by hydrolysis of the resulting product with hydrobromic acid. 2′-Phenyl-2-carboxy-5-chlorodiphenylamine was obtained in good yield by refluxing for two hours a nitrobenzene solution of excess 2-biphenylamine with 2,4-dichlorobenzoic acid, potassium carbonate and a trace of cupric oxide. Treatment of this product with phosphorus oxychloride gave 3-chloro-5-phenylacridone; the desired 3,9-dichloro-5-phenylacridine was obtained from the latter compound by means of phosphorus pentachloride.

3-Chloro-5-phenyl-9-(γ-(N-morphilino) propylamino) acridine was prepared by heating 3,9-dichloro-5-phenylacridine and γ-(N-morpholino) propylamine in phenol at 80-85°. This solid product was converted to its dihydrochloride. Using δ-diethylamino-α-methylbutylamine instead of the morpholinopropylamine gave a yellow oil which was converted to 3-chloro-5-phenyl-9-(δ-diethyl-amino-α-methylbutylamino) acridine dihydrochloride.

Attempts to prepare 2′-phenyl-4′-bromo (or chloro)-2-carboxy-5-chlorodiphenylamine by the condensation of 5-bromo (or chloro)-2-biphenylamine with 2,4-dichlorobenzoic acid were unsuccessful. In this type of reaction the apparent decrease in re-

activity of 2-biphenylamine by halogen substitution was attributed to the lower order of basicity of the halogenated amines.

Chlorination of 2′-phenyl-2-carboxy-5-chlorodiphenylamine yielded a monochloro derivative, 2′-phenyl-4′(?),5-dichloro-2-carboxydiphenylamine. Treatment of this with phosphorus oxychloride gave 3,7(?),9-trichloro-5-phenylacridine directly. A preliminary attempt to obtain 3,7(?)-dichloro-5-phenyl-9-(δ-diethylamino-α-methylbutylamino)acridine was unsuccessful, only 3,7(?)-dichloro-5-phenylacridone being isolated from the reaction.

Bromination of 2′-phenyl-2-carboxy-5-chlorodiphenylamine apparently gave a mixture of isomers; these were not separated but treated with two moles of phosphorus pentachloride. The resulting material was easily purified, but its reactions and a halogen anaylsis indicated that the compound so formed was probably 3,x-dichloro-7(?)-bromo-5-phenylacridone rather than the expected 3,9-dichloro-7(?)-bromo-5-phenylacridine.

Synthetic methods for 5-methoxy-2-biphenylamine are proposed and the results of preliminary, though unsuccessful, experiments in this direction are described.

Crystalline 2-biphenylamine, obtained by cooling freshly distilled commercial material, has been found to exhibit a decided purplish triboluminescence when ground or crushed.

Summary

3-Chloro-5-phenyl-9-(γ-(N-morpholino)propylamino acridine, its dihydrochloride and 3-chloro-5-phenyl-9-(δ-diethylamino-α-methylbutylamino)acridine dihydrochloride have been prepared. Direct chlorination of 2′-phenyl-2-carboxy-5-chlorodiphenylamine yielded a monochloro derivative which is probably 2′-phenyl-4′,5-dichloro-2-carboxydiphenylamine. This has been converted to 3,7(?),9-trichloro-5-phenylacridine and to 3,7(?)-dichloro-5-phenylacridone. Three synthetic methods for 5-methoxy-2-biphenylamine have been attempted without success. Crystalline 2-biphenylamine has been found triboluminescent.

II. *Stereochemistry of 2-Substituted Biphenyls*

Previous investigations[4,6] concerning the resolvability of 2-substituted biphenyls have shown that apparently larger "interference values" than those usually required for resolvability on

the basis of the coaxial-coplanar theory must be necessary. In only one case have stereoisomers been reported;[4] the low rotation observed in this instance still leaves some doubt as to the resolvability of compounds of this type. Although 2,2′-diiodo-4,4′-dicarboxybiphenyl is capable of resolution,[5] all attempts[4,6] to resolve 2-iodo-3′-carboxybiphenyl have failed. It is thought, however, that an increase in the size of the *ortho* substituent may lead to resolvability. This investigation reports the synthesis of 2-iodoso-3′-carbomethoxybiphenyl and a study of synthetic methods for analogous iodoxy compounds.

Experimental

2-Iodo-3′-carboxybiphenyl was prepared by the method of Cairns and Adams,[6] the steps being: preparation of 2-nitro-3′-carboxybiphenyl by the Ullmann procedure using *o*-bromonitrobenzene and ethyl *m*-iodobenzoate, esterification, reduction to the amino ester, saponification, diazotization and replacement of the diazonium group with iodine. By omitting the saponification, 2-iodo-3′-carbomethoxybiphenyl was obtained.

2-Iodoxybiphenyl was prepared from 2-iodobiphenyl in 39 per cent yield by conversion of the latter into its dichloride and hydrolytic oxidation with aqueous sodium hypochlorite. However, this method when applied to *m*-iodobenzoic acid and to 2-iodo-3′-carboxybiphenyl yielded no iododichlorides although esters of these acids readily formed ethyl *m*-I,I-dichloroiodobenzoate and 2-I,I-dichloroiodo-3′-carbomethoxybiphenyl. The latter compound gave 2-iodoso-3′-carbomethoxybiphenyl upon hydrolysis, but this was not converted to the iodoxy compound by sodium hypochlorite.

Chlorination of *m*-iodobenzoyl chloride yielded *m*-I,I-dichloro-iodobenzoyl chloride and hydrolytic oxidation with sodium hypochlorite converted this to the known *m*-iodoxybenzoic acid in 34 per cent yield (from *m*-iodobenzoic acid). This procedure when applied to 2-iodo-3′-carboxybiphenyl was unsuccessful.

Summary

Attempts to prepare 2-iodoxy-3′-carboxybiphenyl from 2-iodo-3′-carboxybiphenyl were unsuccessful although the methods used gave 2-iodoxybiphenyl from 2-iodobiphenyl and *m*-iodoxybenzoic

acid from *m*-iodobenzoic acid in satisfactory yields. 2-Iodo-3′-carbomethoxybiphenyl was converted to 2-I,I-dichloroiodo-3′-carbomethoxybiphenyl and then to 2-iodoso-3′-carbomethoxybiphenyl. The latter, however, could not be oxidized to the corresponding iodoxy ester.

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VITA

The writer was born at Independence, Iowa, on April 27, 1914. After graduation from the high school of that city he entered Coe College, receiving the degree of Bachelor of Arts from that institution in 1936. He continued his work in the Graduate School of the University of Illinois, first in Physics and then in Organic Chemistry. During his residence at the University he held the following appointments: graduate assistant in physics, 1936-1937; Special Research Assistant in Chemistry, 1937-1938; graduate assistant in chemistry, 1938-1940. He is a member of Alpha Chi Sigma, Phi Lambda Upsilon and Sigma Xi.

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